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EXAMINER

EPPERSON, JON D

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 18

Application Number: 09/647,069
Filing Date: September 26, 2000
Appellant(s): BOYMOND ET AL.

M. Herbert B. Keil
For Appellant

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GROUP 2500

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 6, 2003.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

Appellants' statement that there are no related appeals or interferences within the meaning of 37 CFR §1.192(c)(2) is acknowledged.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. Appellants After-Final amendment canceling claims 5-8 has been entered (see Paper No. 17, page 2 paragraph 1; see also page 5, last line).

(5) *Summary of Invention*

The summary of invention contained in the brief is deficient because Appellants do not state that the process for preparing Grignard compounds of formula I "is carried out on a solid support (R5)" as stated in Appellants' amended claim 1 (see Paper No. 11, claim 1, last line). Appellants' invention is now drawn to a "solid-phase" process for preparing Grignard compounds instead of a "solution-phase" process.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-4 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,420,310	OHNO	5-1995
4,254,030	CAPORICCIO	3-1981

Minoura, et al., "Reaction of Poly(vinyl chloride) with Magnesium and Grignard Reagents" J. Polym. Sci., vol. 7, no. 11 (1969), pp. 1701-1703

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohno et al (US 5420310) (Date of Patent is **May 30, 1995**) in view of Minoura et al (*J. Polym. Sci., Part A-1*, 1969, 7(11), 3245-55) and Caporiccio et al (US 4,254,030) (Date of Patent is **March 3, 1981**).

Ohno teaches the same magnesium-halogen exchange reaction disclosed by the applicant, which reads on claims 1-4 (see summary of reference as set forth in *Claim Rejections - 35 USC § 102* in Paper No. 10). Please note that the summary of the reference is reproduced in brackets below:

[Ohno et al discloses a process for the preparation of Grignard compounds reading on the claimed method of preparing compounds of general formula I using an aromatic halide of general formula II and a Grignard reagent of general formula III (compare claim 1 to Ohno et al, column 8, reaction A-2 and column 10, second paragraph). Ohno et al discloses as the Grignard reagent i.e., applicant's compound III (see claim 1), "ethyl magnesium bromide, n-propyl magnesium bromide, isopropyl magnesium bromide, [etc.]", which reads on *claim 1* (see Ohno et al column 10, second paragraph, which reads on the claimed compound III where $R^4 = \text{alkyl}$ and $X = \text{halogen}$). Ohno et al discloses as the aromatic halide i.e., applicant's compound II (see claim 1), compound 2, which reads on *claim 1* with $R^1 = \text{halogen}$; $X^a = \text{Br}$; $\{B, D, \text{ and } E\} = \text{CH}$ or attachment point for Mg-X ; and $\{A \text{ and } F\} = \text{CR}^2$ whereby A and F form a five membered ring with "O" as the heteroatom (see claim 1 stating, "it being possible for two adjacent variables A, B, D, E or F together to form another substituted or unsubstituted aromatic saturated or partially saturated ring which has 5 to 8 atoms in the ring and which may contain one or more heteroatoms such as O, ..."). Finally, the dioldibromide, compound 2, "reacted with a Grignard reagent [e.g., isopropyl magnesium bromide] to exchange the bromine *only* on the 5th position of Compound 2 for magnesium halide" leaving the other bromine intact, which reads on *claim 1* (see applicant's general formula

Art Unit: 1639

I) with R^1 = halogen; $X = Br$; {B, D, and E} = CH or attachment point for Mg-X; and {A and F} = CR^2 whereby A and F form a five membered ring with "O" as the heteroatom (see above).

Ohno et al also discloses preparing said Grignard reagents in an aprotic solvent such as "ether, tetrahydrofuran (THF), 1,2-dimethoxyethane (DME) and dioxane", which reads on *claim 2* (compare claim 2 to Ohno et al, column 10, lines 60-61).

Ohno et al also discloses preparing said Grignard reagents at temperatures below $-15^{\circ}C$ such as at "temperatures ranging from -40° to $30^{\circ}C$, preferably -20° to $0^{\circ}C$ ", which reads on *claim 3* (compare claim 3 to Ohno et al, column 10, lines 63-64).

Ohno et al also discloses preparing said Grignard reagents within 10 hours, which reads on *claim 4* (compare claim 4 to Ohno et al, see example 11 column 29, lines 1-4 and 41-47).]

However, Ohno lacks the teaching of carrying out the magnesium-halogen exchange reaction on a solid support as recited in the currently amended claims.

However, Minoura *et al* (J. Polym. Sci., Part A-1, 1969, 7(11), 3245-55) teaches the synthetic usefulness of performing a magnesium-halogen exchange reaction on a solid support using poly(vinyl chloride) as the solid support and benzylmagnesium chloride as the compound of general formula III (see Minoura et al, page 3249, reaction 5). Caproiccio et al also teaches the synthetic usefulness of performing a magnesium-halogen exchange reaction on a solid support using copolymers of fluorosulphonyl olefins (see Caproiccio et al, column 3, reaction V).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the

art to carry out the magnesium-halogen exchange reaction described by Ohno et al on a solid support, as taught by Minoura *et al.* One would have been motivated to use a magnesium-halogen exchange reaction on a solid support to obtain higher yields that are “free of by-products, avoiding any interaction between ... [functionalities that are labile to Grignard reagents] and Grignard compounds, [and] ... also avoiding secondary reactions between the different species present during the course of the reaction” (see Caproiccio et al, column 8, lines 22-29). One would have had a high expectation of success since both Minoura et al and Caproiccio et al teach that magnesium-halogen exchange reactions can occur for reactions involving alkyl halides on a solid support.

(11) Response to Argument

First, the examiner would like to state that the summary of the Examiner's Rationale found on pages 3-4 of the Brief is not correct. First, the Examiner notes that Appellants failed to address the point that both the Minoura and Caproiccio references disclose “magnesium-halogen exchange reactions” on a “solid-support”, which clearly demonstrates that performing solid-phase reactions of this type was well established in the art at the time of filing. Second, the Examiner notes that the motivation to combine the references was not drawn to obtaining “higher yields” alone as purported by Appellants (see Paper No. 16, page 4, paragraph 1), but rather obtaining “higher yields” of “pure” products that result from a facile solid-phase synthesis work-up procedure (i.e., see rejection above, “One would have been motivated to use a magnesium-halogen exchange reaction on a solid support to obtain higher yields that are ‘free of by-products’”) (emphasis added on “free of by-products”, which indicates that the products are

Art Unit: 1639

“pure” or “clean”).

Argument 1: Appellants argue, “Furthermore, the prior art references do not teach or suggest all the claim limitations together” (see Paper No. 16, page 8, paragraph 2, last sentence).

Response 1: The Examiner contends that the combined references do teach and/or render obvious all the claimed limitations as outlined in the 35 U.S.C. § 103(a) rejection above. Furthermore, the Examiner notes that Appellants do not provide any rationale or reasoning to support their statement.

Argument 2: Appellants argue, “In effect the examiner has chosen to combine these three references with the hindsight of the applicants specification. However, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention” (see Paper No. 16, paragraph bridging pages 8-9).

Response 2: In response to Appellants’ argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Argument 3: Appellants argue, “Furthermore, a single line in a reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness ... That is, the examiner utilizes the statement that higher yields are obtained in Caporiccio to support the obviousness rejection in the instant invention which produces different materials than that of

Art Unit: 1639

Caporiccio. Caporiccio discusses fluorosulphonyloxafluoroalkanes and their reactions with Grignard compounds. In contrast to that of Caporiccio, the instant invention produces the five or six-membered residue as claimed in claim 1, formula 1" (see Paper No. 16, page 5, paragraph 2).

Response 3: First, the Examiner notes that Appellants have misconstrued the Examiner's argument (see rejection above). The motivation to combine the references was not drawn to obtaining "higher yields" alone as purported by Appellants, but rather to obtaining "higher yields" of "pure" products that results from a facile solid-phase synthesis work-up procedure (see rejection above, "One would have been motivated to use a magnesium-halogen exchange reaction on a solid support to obtain higher yields that are 'free of by-products'") (emphasis added on "free of by-products").

Second, the Examiner notes that the "hindsight reasoning" argument was adequately addressed in Response 2 above (which is incorporated in its entirety herein by reference).

Third, the Examiner notes that a single line in a references has not been "taken out of context" as purported by Appellants. Appellants state that Caporiccio only provides motivation to synthesize the compounds disclosed in Caporiccio apparently at the exclusion of all other compounds (see Paper No. 14, page 5, "the examiner utilizes the statement that higher yields are obtained in Caporiccio to support the obviousness rejection in the instant invention which produces different materials than that of Caporiccio"). The Examiner contends that this interpretation of Caporiccio is too narrow and further fails to appreciate the teachings of Minoura. For example, both Caporiccio and Minoura demonstrate that magnesium-halogen exchange reactions can be performed on a solid support (see 35 U.S.C. § 103(a) rejection). Thus a person of skill in the art would have concluded that "any" magnesium-halogen exchange

Art Unit: 1639

reaction could be performed on a solid-support with similar benefits (i.e., higher yields of purer products) because these reactions are highly predictable (i.e., the reactions have been known since the early 1900's and mechanism of action is well established) and the Examiner has set forth "two" examples that fall within this category. Consequently, the cited reference has not been "taken out of context" because the teachings of Caporiccio and Minoura would extend to the compounds of Ohno.

In addition, the Examiner notes that Appellants have not provided any reason or scientific evidence to demonstrate why a person of skill in the art would not conclude that they could extend the teachings of Caporiccio and Minoura to the compounds of Ohno. That is, Appellants have not set forth any reason why they would expect the magnesium-halogen exchange reactions disclosed by Ohno to act any differently than the magnesium-halogen exchange reactions disclosed by Minoura and Caporiccio.

Argument 4: Appellants argue, "Utilizing the general statement that Caporiccio suggests that higher yields may be obtained the examiner seems to utilize an "obvious to try" standard of invention ... A general statement that one reaction produces higher yields cannot supply motivation to combine references. This argument is similar to a case in which the Federal Circuit found that no suggestion to modify the prior art existed." (see Paper No. 16, pages 6-7, especially page 6, paragraph 2).

Response 4: The Examiner contends Appellants' "obvious to try" argument is not persuasive since ample motivation to combine the references has already been provided in the 35 U.S.C. § 103(a) rejection (see rejection above). The Examiner further notes that Ohno relates to a "manufacturing process" for PGI2 derivatives (see Ohno, column 1, lines 11-12) and, as a

Art Unit: 1639

result, obtaining the highest yield of “pure” products would be of the utmost importance. Thus, references that explicitly teach ways to increase the yield of “purity products” in any one of the method steps of the PGI2 “manufacturing process” represent more than just a “general statement” of motivation. Here, both Caporiccio and Ohno provide “specific” guidance for increasing the yield of “pure” products in the “A-2” step of the PGI2 manufacturing process (see Ohno, bottom of column 8 and bottom of column 10 disclosing the “A-2” step). This represents a “specific” teaching and, as a result, the *In re Fine* case does not apply.

In addition, the Examiner further notes that there are three possible sources for motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998). In addition to the “prior art” motivation mentioned above, the Examiner contends that the “knowledge of persons of ordinary skill in the art” would also provide adequate motivation here because as previously stated “motivation for cleaner products and higher yields was well known to those of skill in the art at the time of filing [for] performing any solution based organic chemistry reaction on a solid support” including the magnesium-halogen exchange reaction disclosed by Appellants (see Paper No. 14, page 6, paragraph 1).

Argument 5: Appellants argue, “the examiner has failed to show that the applicants had an expectation of success ... these references [Minoura et al and Caporiccio et al] do not suggest the success of the instant invention. The examiner seems to import an “obvious to try” standard as the standard for obviousness” (see Paper No. 16, page 7, paragraph 2).

Response 5: The Examiner contends as stated in the previous office action a reason that

Art Unit: 1639

one of skill in the art would expect to be successful:

One would have had a high expectation of success since both Minoura et al and Caporiccio et al teach that magnesium-halogen exchange reactions can occur for reactions involving alkyl halides on a solid support

(see 35 U.S.C. §103(a) rejection). The reactions as taught by Minoura and Caporiccio both employ Grignard reagents on solid-phase that operate under the exact same “mechanism” as those disclosed by Appellants i.e., a magnesium-halogen exchange reaction. These Grignard reactions have been known in the art since the early 1900’s and the mechanism of reaction is well established (see Paper No. 14, page 10, “References Illustrative of the State of the Prior Art” section, especially Solomons, G. T. W. reference cited therein). Furthermore, Appellants have not set forth any reasons or scientific data that would indicate why the magnesium-halogen exchange disclosed by Minoura and Caporiccio is “unpredictable”, which would prevent its extension to the magnesium-halogen exchange reactions disclosed by Ohno.

The Examiner further notes that obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a “reasonable expectation of success.” In re O’Farrell, 853 F.2d at 903-904 [7 USPQ2d at 1681].

Finally, the Examiner further notes that the “obvious to try” issue was adequately addressed in “Response 4” above (which is incorporated in its entirety herein by reference).

Argument 6: Appellants argue, “In further support of this argument the examiner argues that the Grignard reactions are well known since the early 1900’s and the mechanism of the reaction is well established. However, this appears to ignore the literature that outlines the difficulty of obtaining the instant invention. For example, the inventors report that very few functionalized organomagnesium reagents have been prepared due to the low functional-group

Art Unit: 1639

tolerance of these reagents ... Furthermore, the inventors state in the specification that the drastic conditions of the procedures under the prior art do not permit other functional groups, such as esters or nitrile moieties, which are able to react with a Grignard compound as electrophile to be retained in the molecule, because oligomerization, reduction or other side reactions would occur” (see Paper No. 16, page 8, paragraph 2).

Response 6: The Examiner contends that the combined references teach Appellants’ preferred “conditions” for avoiding unwanted side reactions and, as a result, Appellants arguments are moot (e.g., see Paper No. 14, page 3, paragraph 6, especially 35 U.S.C. § 102(b) rejection in Paper No. 10 cited therein at paragraphs bridging pages 6-7, which discloses the use of “aprotic solvents” and “low temperatures”; compare with Appellants’ preferred conditions listed on page 12, paragraph 2 of the Specification). Furthermore, the Examiner notes that both Ohno and Caporiccio disclose the use of “low tolerant” functional groups that would ordinarily react with a Grignard reagent if the lower temperatures and aprotic solvents disclosed in those references were not used (e.g., see Ohno et al, column 8, compound 2, which contains “two” bromines wherein one of the “labile” bromines does not react; see also Caporiccio et al, column 3, compound 5 disclosing a “labile” FSO₂ group that does not react). Therefore, Appellants statement that “the drastic conditions of the procedures under the prior art do not permit other functional groups ... which are able to react with a Grignard compound as electrophile to be retained in the molecule, because oligomerization, reduction or other side reactions would occur” (see Paper No. 16, page 8, paragraph 2) is inaccurate because both Ohno and Caporiccio disclose “less drastic conditions” (e.g., use low temperatures) that do permit “low tolerant functional groups” (i.e., halogens and FSO₂) to exist in the molecule. Therefore, Appellants assessment of

the state of the prior art is wrong.

Argument 7: Appellants state, "the examiner has failed to establish a prima facie case of obviousness. The references cited by the examiner do not provide a suggestion or motivation to combine the teachings to produce the instant invention. As noted above, the examiner suggests that one of ordinary skill in the art would have been motivated to produce the instant invention because Caporiccio suggests that higher yields may be obtained. However, the citation that higher yields may be obtained refers to a process that does not produce compounds of the formula I, nor does it involve compounds of formula II" (see Paper No. 16, pages 4-5, especially page 4, last paragraph).

Response 7: The examiner respectfully disagrees with this assessment. First, the Examiner notes that Appellants have misconstrued the Examiner's argument (see rejection above). The motivation to combine the references was not drawn to obtaining "higher yields" alone as purported by Appellants (see Paper No. 16, sentence bridging pages 4-5, "As noted above, the examiner suggests that one of ordinary skill in the art would have been motivated to produce the instant invention because Caporiccio suggests that higher yields may be obtained"), but rather obtaining "higher yields" of "pure" products that results from a facile solid-phase synthesis work-up procedure (see rejection above, "One would have been motivated to use a magnesium-halogen exchange reaction on a solid support to obtain higher yields that are 'free of by-products'") (emphasis added on "free of by-products").

Second, in response to Appellants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In*

Art Unit: 1639

re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Appellants fail to appreciate that Ohno does teach Appellants' compounds of formula I & II and, as a result, the combination of references also teaches said compounds (see Paper No. 14, page 5-6 wherein this argument was previously addressed).

Third, in response to appellants' argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Examiner argued in the 35 U.S.C. § 103(a) rejection that:

One would have been motivated to use a magnesium-halogen exchange reaction on a solid support to obtain higher yields that are "free of by-products, avoiding any interaction between ... [functionalities that are labile to Grignard reagents] and Grignard compounds, [and] ... also avoiding secondary reactions between the different species present during the course of the reaction" (see Caporiccio et al, column 8, lines 22-29).

Consequently, a motivation to synthesize the compounds of Ohno on a solid-support as taught by Caporiccio and Minoura was properly cited. The motivation for higher yields of cleaner products was well known to those of skill in the art at the time of filing for performing any solution based organic chemistry reaction on a solid-support. However, in the interests of providing a specific reference that teaches this motivation not only for organic chemistry reactions in general, but for Appellants' claimed magnesium-halogen exchange reactions, the Examiner has set forth two examples (i.e., Caporiccio and Minoura) wherein magnesium-halogen exchange reactions were performed on a solid-support. Therefore, the motivation to obtain cleaner products in higher yields with a facile workup using magnesium-halogen

Art Unit: 1639

exchange reactions on solid-support was well known in the art at the time of filing (see Paper No. 14, page 5-6 wherein this argument was previously addressed).

Therefore, the examiner maintains that the combined teachings of the cited references render the claimed invention obvious. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Here, the beneficial result of the combination of references is the advantage of easy work-up procedures that would result in higher yields of cleaner products.

Argument 8: Appellants argue, "Alternatively, even if a prima facie case of obviousness has been established applicant have overcome this showing with the showing of unexpected results. Proof of an unexpected improvement may rebut a prima facie case of obviousness ... Data to support this improvement is set forth in applicant's specification in Tables I and II. The results as set forth in Table II produced a yield of free product of usually 90% or more" (see Paper No. 16, page 9, paragraph 2).

Response 8: The Examiner contends that any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (In MPEP § 716.02). The Examiner notes that Appellants have not provided a "side-by-side" comparison to make this determination. Furthermore, the combined teachings of Caporiccio, Minoura and Ohno set forth Appellants'

Art Unit: 1639

preferred reaction conditions (i.e., aprotic solvents and low temperatures) and, as a result, would be expected to produce the same results. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the appellants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For the above reasons, it is believed that the rejections should be sustained.


Respectfully submitted,

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December 22, 2003

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